REMARKS

Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested. Claims 1, 8-10, 13-15, 20, and 24-30 have been canceled without prejudice. Claims 2 and 4 have been amended to depend from claim 5. Claim 5 has been rewritten in independent form and amended to recite that the tumor cells are from the patient (see the Specification, page 18, lines 15-16). Claim 16 has been amended to recite "intravenously administering" (Specification, page 10, lines 17-18). No new matter has been added. Accordingly, claims 2-7, 11-12, 16-19, 21-23, and 31 are pending and at issue.

35 U.S.C. §112, 1st Paragraph - Enablement

Claims 1-31 stand rejected for alleged lack of enablement. Each of the Examiner's rejection under this statue is addressed separately below.

Briefly, the Examiner agrees that the specification is enabled for suppressing tumor growth in mice, but contends that it does not provide for the suppression of tumor growth in humans. The Examiner further contends that it is inappropriate to use the references of DNA vaccination as support for RNA vaccination for immune tolerance induction and for immunization against any and all pathogens.

Applicant respectfully disagrees. The claims have been amended to focus on immunotherapy of tumors using total tumor cell RNA from the tumor of the patient receiving treatment (Applicant reserves the right to prosecute the unclaimed subject

matter of the cancelled claims in a related continuation application). Applicant respectfully submits that the evidence of record, and provided herewith, establishes the predictability of animal models of immunization for human immune responses *when immunization is with nucleic acids*. Thus, contrary to the Examiner's contention, the evidence in the Rule 132 Declaration is highly probative of enablement of the claimed invention.

Recent publications have confirmed the feasibility of inducing tumor antigen-specific immune responses in patients with metastatic cancer using total tumor RNA-loaded dendritic cells ((*Induction of Tumor-Specific Cytotoxic T Lymphocytes in Cancer Patients by Autologous Tumor RNA-Transfected Dendritic Cells*, Nair et al., 2002 Ann of Surg, 235;4:540-9; "Nair"; copy attached as Exhibit A). Nair reports that dendritic cells pulsed with total tumor cell RNA of autologous tumors elicited antigen-specific T cell responses in humans (see Abstract), as they had seen in mice (see page 541, first column). Thus, as with other nucleic acid vaccine approaches, the results of administration of a total RNA vaccine in humans (albeit using a very different approach than that claimed here) parallel the results in animal studies. Accordingly, one of ordinary skill in the art would have no reason to doubt the veracity of the teachings of the instant application, or the applicability of the results obtained in mice to the results that would be achieved in humans.

As stated in the Response After Final of April 23, 2002, much literature at the time of the invention has shown induction of potent immunity with DNA-based

vaccines. The references cited in that response have shown the correlation of the use of DNA in both animals and humans. Similarly, Nair demonstrates the efficacy of RNA-based vaccines in humans. Nair showed tumor-immune responses induced in a patient with a carcinoembryonic antigen-expressing adenocarcinoma after immunization with autologous dendritic cells transfected with total tumor RNA.

As shown in the references and stated in the Response After Final, DNA vaccines have been shown effective in both animals and humans. Thus, since RNA has been shown effective in animals, one skilled in the art can deduce RNA would be effective in humans as stated in the present invention. The Examiner In addition, with respect to dendritic cells transduced with tumor RNA, the effectiveness of this method in generating anti-tumor immunity is disclosed in the present application.

The Examiner contends that one skilled in the art could not use the results from tumor RNA to predict the effect of other types of antigen RNA's without undue experimentation and that the administration of total tumor RNA would not circumvent the problem and that it is inappropriate to use the references of DNA vaccine for tumor or influenza virus as evidence for RNA vaccination for microbial, allergen, autoantigen, or transplantation antigen. In view of the amendment of the claims, this basis for the rejection is moot.

The test for enablement is whether a person who is reasonably skilled in the art could make and use the claimed invention without undue experimentation, using the disclosure in the patent coupled with information that was known when the

patent application was filed. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The proper test is not, therefore, whether any experimentation would be necessary, but instead, if experimentation would be necessary, whether it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). See, also, *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The argument submitted in the Response After Final and the accompanying Declaration Under Rule 132 of Dr. Richard Granstein are incorporated herein. With regard to tumor immunity, the literature submitted in support of the Response After Final showed an induction of potent immunity with DNA-based vaccines, and that dendritic cell immunization provides protection against established tumors. The supporting literature also demonstrated that a DNA vaccine had been shown effective against influenza and the immunization of mice using DNA encoding various bacteria, thus showing the use of genetic immunization for immunity against multiple microbial antigens. The accompanying Nair publication establishes the predictability of the experimental results in the present application with total RNA vaccines in humans.

As stated in *In re Angstadt*, the question is not whether any experimentation would be necessary, but instead, if experimentation would be

necessary, whether it is undue. A person reasonably skilled in the art could make and use the claimed invention without undue experimentation, using the disclosure in the instant application coupled with information that was known when the patent application was filed. Thus by extrapolating the results of Bacci in combination with the state of the art at the time of the invention and the teachings in the specification, i.e. the efficacy of reducing the rate of tumor growth in two mouse tumor models, one skilled in the art could use the results from tumor RNA to predict the effect of other types of antigen RNA's, and thus the specification is enabling.

The Examiner contends that there is insufficient support commensurate with the scope of the claim to indicate that any pathogen cellular total RNA would survive with the intravenous delivery and mount a sufficient immune response.

In response, the claims have been amended to recite total tumor cell RNA. Support can be found in the specification at Example 4. Thus, the applicant believes this amendment overcomes the rejection.

The Examiner also contends that the specification teaches that anti-tumor stimulation, not tolerance, was achieved by intradermal administration, whereas intravenous injection of tumor RNA induced tolerance and that the claims drawn to tolerance, i.e. claims 16-23, are not limited to intravenous administration.

Claim 16, which is directed to inducing immune tolerance, has been amended to recite a method comprising "intravenously administering antigen RNA..." (emphasis added). Thus, since the specification teaches that intravenous injection of

tumor RNA induced tolerance as stated by the Examiner, the specification is now commensurate with the scope of the claims. (Note that independent claim 5 recites administration of the immune-stimulating tumor vaccine to epidermal cells, i.e., not by intravenous administration, and thus the Examiner's comments with respect to the route of administration – page 4 of the Office Action – are not pertinent to claim 5 or claims dependent thereon.)

In response to the Examiner's contention that the immune response was limited to the types of tumor cells, Applicant has amended claim 5 to recite that the total cell RNA is obtained from tumor cells from the patient to be treated, thus obviating the Examiner's basis for rejection on pages 8-9 of the Office Action.

The Examiner contends that what shows effective in a mouse is not predictable in humans. The applicant respectfully disagrees. The current literature available is indicative that responses in mice correlate to responses in humans and thus the statements made in the instant disclosure are likely to be true. However, the results in Nair demonstrate that the Examiner's position is not well founded in this case.

Nair evaluated the hypothesis that human dendritic cells loaded with the total RNA content of autologous tumor cells could stimulate a cytotoxic T lymphocyte response (*Induction of Tumor-Specific Cytotoxic T Lymphocytes in Cancer Patients by Autologous Tumor RNA-Transfected Dendritic Cells*, Nair et al., 2002 Ann of Surg, 235;4:540-9). The hypothesis was based on vaccination of mice with dendritic cells

loaded with peptide or protein antigens results in tumor-specific cytotoxic T lymphocyte responses capable of rejecting implanted tumors and the fact that the feasibility of loading dendritic cells with antigen by transfecting the dendritic cells with the mRNA encoding that antigen had previously been shown. Nair also states that the advantage of transfecting dendritic cells with RNA encoding antigen is that mRNAs encode multiple epitopes that can bind to many HLA alleles. Nair observed that treatment of tumor-bearing animals with dendritic cells pulsed with tumor-derived RNA leads to a significant reduction in lung metastasis. Based on the success of these studies, Nair initiated tests on humans and has shown the induction of primary, carcinoembryonic antigen-specific cytotoxic T lymphocytes using human dendritic cells transfected with carcinoembryonic antigen RNA.

As pointed out above, strong correlation exists between studies of nucleic acid-based vaccines performed in mice and those in humans. The references submitted in support of the previously filed Response After Final show the correlation of the use of DNA-based vaccines used in mice were highly effective when used in humans. The additional references submitted with this amendment extend this to RNA-based vaccines. Thus, unlike the general situation where results in mice are suggestive, but not necessarily predictive of the human response, with nucleic acid-based vaccines, the murine response is highly informative of human. Accordingly, the murine models disclosed in the specification are, and would be regarded by one of skill in the art as, predictive of the results in humans.

Since the claimed invention is effective in reducing the rate of tumor growth in two mouse tumor models, it is highly predictable to have the same effect in humans.

Applicant has met the requirements of 35 U.S.C. §112. Applicant has provided credible scientific evidence in the form of literature at the time of the invention and has amended the claims in accordance with the enablement requirement. The present specification enables one of skill how to use the claimed invention and provides a reasonable degree of assurance of success in practicing the full scope of the claimed invention.

Thus, in view of the previously filed Response After Final, arguments of record, and evidence presented herein, applicant submits that the specification provides full enabling support for the claimed invention. Applicant respectfully requests that the 35 U.S.C. §112 rejection be withdrawn.

35 U.S.C. §112, 2nd Paragraph - Indefiniteness

The Examiner has rejected claims 1-17, 11, 12, and 16-31 for alleged indefiniteness. Each of the Examiner's rejection under this statue is addressed separately below.

The Examiner has rejected claims 16-23 as being vague and ambiguous contending that claims 16-23, which are drawn to inducing immune tolerance to an antigen, have an opposite effect than claims 1-7, 11, 12, and 31, allegedly drawn to

inducing an immune response to an antigen using any route of administration (the latter is not an accurate statement of the claims, which require administration to epidermal cells and thus exclude, e.g., intravenous administration). The Examiner concludes that the opposite effect creates ambiguity since it is unclear how such opposite effects can be achieved.

In response, the applicant has amended independent claim 16 to recite that the method comprises intravenously administering antigen RNA. Thus, claims 16-23 are drawn to inducing immune tolerance to an antigen using solely intravenous administration. In distinction to the tolerance-inducing methods, claims 2-7 and 31 comprise administering total tumor cell RNA to epidermal cells to induce an immune response.

In addition, claims 16-23 are directed to inducing solely an immune tolerance, whereas claims 2-7, 11, 12, and 31 are directed to inducing an immune response. The specification at page 13 defines the term "tolerize" to mean "induce immunological tolerance", which "is the avoidance of or suppression of a specific immune response." Thus, claims 2-7, 11, 12, and 31 are directed to inducing a response, whereas claims 16-23 are directed only to avoiding or suppressing a specific immune response.

Thus, intravenous administration of antigen RNA to induce an immune tolerance would cause different effects than epidermal administration of total tumor

cell RNA to induce an immune response. Therefore, the applicant respectfully requests withdrawal of this rejection.

The Examiner has rejected claim 16 as being vague and ambiguous contending that the "subject" of the antigen RNA administration has not been identified in the claim.

In response, the applicant has amended the claim to recite that the subject is a "patient". Thus, claim 16 provides for "a method of inducing immune tolerance to an antigen in a patient" and overcomes the rejection.

The Examiner has rejected claims 24-27 as being vague and ambiguous contending that claim 24 recites a tumor antigen, whereas dependent claims 25-27 recite an autoantigen, an allergen, and a transplant antigen without a sufficient antecedent basis for such recitation.

Applicant has canceled claims 24-27 without prejudice, thus obviating this rejection made by the Examiner.

Thus in view of the above arguments and amendments, the Applicant respectfully requests that this rejection be withdrawn.

35 U.S.C. §102(b) - Anticipation

Claims 24 and 30 stand rejected as being anticipated by Quip et al. (Gene There 1996;3:262-68). The Examiner has also rejected claims 24 and 30 as being anticipated by Corny et al. (Cancer Rees 1995;55:1397-1400).

Applicant has canceled claims 24 and 30 without prejudice, thus obviating this rejection made by the Examiner. Thus the Applicant respectfully requests that this rejection be withdrawn.

35 U.S.C. §103(a) - Obviousness

The Examiner has rejected claims 1-3, 5, 7-9, 13-14, 24, and 28-31 as being obvious over Ashley et al. (J Exp Med 1997 Oct;186:1177-82) in view of Beissert et al. (J Immunol 1995;154:1280-86).

The Examiner alleges that Ashley teaches a method for treating brain tumors comprising pulsing an antigen presenting cell in vitro with RNA. The Examiner also alleges that Beissert teaches that Langerhans cells are dendritic antigen-presenting cells that reside in the epidermis and that they are indicated in tumor immunity. Thus, the Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the method taught by Ashley, by selecting the epidermal cells and the antigen-presenting cells of choice as taught by Beissert.

The Applicant respectfully traverses the above rejection. To establish a *prima facie* case of obviousness, the prior art must teach, motivate, or suggest a skilled artisan to modify a reference or to combine references, and it must provide a reasonable expectation of success in making the claimed invention if the references are combined. Contrary to the Examiner's assertion, it would not have been obvious, at the time the invention was made, to combine the teachings of the references, and

furthermore, were the teachings to be combined, there is still no suggestion to administer a total RNA vaccine to epidermal cells.

Ashley teaches a method for treating brain tumors. Ashley recites that the brain is a unique site where central nervous system tumors do not respond to immunotherapy protocols that are successful systematically (page 1177, left side). Ashley teaches using bone-derived dendritic cells as being effective in brain tumor models (page 1177, left side).

Beissert recites that Langerhans cells are dendritic cells that reside in the epidermis (page 1280, 1st paragraph). It is well-known in the art that Langerhans cells are immature dendritic cells. They are circulating precursors that migrate into the epidermis. Upon uptake of antigen with activation signals, the Langerhans cells migrate to the lymph and mature into antigen-presenting dendritic cells.

Thus, since Ashley teaches the use of bone-derived dendritic cells as the antigen-producing cell to be effective against tumors in the central nervous system, an area where tumors normally do not respond to immunotherapy protocols that were successful systematically, it would not have been obvious to combine the teachings of Beissert and use epidermal cells or immature dendritic cells, *i.e.*, Langerhans cells, as the antigen producing cell to be effective in brain tumors. Thus, there is no suggestion in either reference to administer total RNA to epidermal cells, much less any reasonable expectation that such an approach would work. Therefore, the applicant respectfully requests withdrawal of this rejection.

Furthermore, were the references to be combined, the combined teaching would only suggest substituting the bone-derived dendritic cells of Ashley with the Langerhans cells (possibly with maturation signals) of Beissert. Neither reference contains the suggestion to introduce a total RNA vaccine to epidermal cells, or provides a reasonable expectation that such an approach would be successful in eliciting immunity to a tumor. The Examiner's attention is directed to the Specification at page , which discussed the advantages of administering a total RNA vaccine to epidermal cells instead of dendritic cells, as taught by the prior art of record.

The Examiner has rejected claims 1-3, 5, 7-9, 13-14, 24, and 28-31 as being obvious over Nair et al., U.S. Patent No. 5,853,719, in view of Beissert et al. (J Immunol 1995;154:1280-86). The Examiner has also rejected claims 1-3, 5, 7-9, 13-14, 24, and 28-31 as being obvious over Nair et al., U.S. Patent No. 6,306,388, in view of Beissert et al. (J Immunol 1995;154:1280-86). The Nair '388 patent is a continuation of the Nair '719 patent and contains a substantially identical disclosure. Consequently, they will be addressed as a single cumulative reference (hereinafter the "Nair Patents").

The Examiner states that the Declaration previously submitted under Rule 131 (paper #6) could not be used to antedate the cited patents. The applicant respectfully directs the Examiner to the Rule 131 Declaration (paper #6). The Declaration was submitted to overcome a 35 U.S.C. §102(a) rejection issued in an

office action mailed June 20, 2001. The rejection was based on a published article by Zhang et al. (Hum Gene Ther 1999 May 1;10:1151-61). The article is not a U.S. patent or patent application claiming the same patentable invention as the present application (37 C.F.R. §1.131). The Examiner has not re-issued the 102(a) rejection based on Zhang et al.

Furthermore, the Nair Patents enjoy an earliest effective filing date of April 30, 1996 under 35 USC 120. The Rule 131 Declaration does not purport to antedate this date (although Applicant reserves the right to do so in the future). Moreover, the Nair Patents are not directed to the same invention as the pending claims, so they are available, if at all, under 35 USC 102(e), not 102(g).

Thus, we will now address the 103(a) rejections based on the Nair Patents.

The Applicant has canceled claims 1, 8-9, 13-14, 24, and 28-30 without prejudice, thus obviating these rejections made by the Examiner.

Claims 2-3, 5, 7, and 31 stand rejected over the Nair Patents in view of Beissert. The Examiner contends the '719 patent teaches a method of comprising pulsing an antigen presenting cell in vitro with RNA obtained from a tumor cell or pathogen cell RNA, but does not teach using epidermal cells as the antigen presenting cell. The Examiner further contends that the '388 patent further claims the total tumor RNA and other pathogen RNA.

The Examiner alleges that Beissert teaches that Langerhans cells are dendritic antigen-presenting cells that reside in the epidermis and that they are indicated in tumor immunity. Thus, the Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the method taught by the Nair patents, by selecting the epidermal cells and the antigen-presenting cells of choice as taught by Beissert.

Applicant respectfully traverses this rejection. As discussed above, Langerhans cells are merely a variant of dendritic cells. Nothing in Beissert provides any motivation to substitute Langerhans cells for the cells in Nair, but even if there were such motivation, for the reasons explained above, one would merely use the Langerhans cells of Beissert in the methods of the Nair Patents. Such substitution neither suggests nor provides a reasonable expectation of successfully introducing a total RNA vaccine to *epidermal* cells, as claimed in the pending application.

For an obviousness rejection to be valid, the references themselves must provide a skilled artisan with some suggestion or motivation to combine them. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on the applicants disclosure." M.P.E.P. §706.02(j). It is quite clear that the only motivation to modify Beissert and Nair to administer a total RNA vaccine to epidermal cells comes from the Applicant's disclosure, since the references themselves provide no such motivation. Hindsight reconstruction based on the Applicant's disclosure is error.

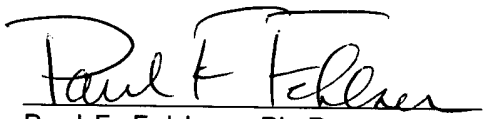
Thus, since there is no motivation or suggestion to combine the prior art references, much less any suggestion to substitute epidermal cells of the dendritic, e.g., Langerhans, cells the references disclose, the applicant respectfully requests that this rejection be withdrawn.

* * *

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case be passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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Marked-Up Claims
Accompanying May 13, 2003 Amendment
U.S. Serial No. 09/484,108
(Docket No. 2650/1F966-US2)

2. (Amended) The method of claim [1] 5 wherein the total cell RNA is administered to the epidermal cells *in vitro*.

4. (Amended) The method of claim [1] 5 wherein the total cell RNA is administered directly into the epidermal cells of the [recipient] patient *in vivo*.

5. (Amended) [The] A method [of claim 1, wherein the pathogen is] of inducing an immune response to a tumor in a patient comprising administering to epidermal cells of the patient total tumor cell RNA in an amount effective to elicit an immune response against the tumor, wherein the tumor cell RNA is from tumor cells from the patient.

16. (Twice Amended) A method of inducing immune tolerance to an antigen in a patient, which method comprises intravenously administering antigen RNA in an amount effective to elicit immune tolerance against the antigen.

Pending Claims
Accompanying May 13, 2003 Amendment
U.S. Serial No. 09/484,108
(Docket No. 2650/1F966-US2)

2. The method of claim 5 wherein the total cell RNA is administered to the epidermal cells *in vitro*.

3. The method of claim 2 wherein the epidermal cells are modified by pulsing the cells with the total RNA.

4. The method of claim 5 wherein the total cell RNA is administered directly into the epidermal cells of the recipient *in vivo*.

5. A method of inducing an immune response to a tumor in a patient comprising administering to epidermal cells of the patient total tumor cell RNA in an amount effective to elicit an immune response against the tumor.

6. The method of claim 5, wherein the tumor is a fibrosarcoma tumor.

7. The method of claim 1, wherein the immune response reduces or inhibits growth of the pathogen.

11. A method for protecting a subject from a cancer which method comprises delivering an immunologically effective amount of total tumor cell RNA to the subject, wherein the tumor cell is of the type associated with the cancer.

12. The method of claim 11, further comprising delivering an immunostimulatory amount of an immune activating or inflammatory cytokine to the subject.

16. A method of inducing immune tolerance to an antigen in a patient, which method comprises intravenously administering antigen RNA in an amount effective to elicit immune tolerance against the antigen.

17. The method of claim 16, wherein the RNA is total cellular RNA from tissues containing the antigen.

18. The method of claim 16, wherein the RNA is total cellular mRNA from tissues containing the antigen.

19. The method of claim 16, wherein the RNA is mRNA encoding the antigen.

21. The method of claim 16, wherein the antigen is an autoantigen.

22. The method of claim 16, wherein the antigen is an allergen.

23. The method of claim 16, wherein the antigen is a transplant antigen.

31. A method for protecting a subject from a cancer which method comprises delivering to epidermal cells of a subject an immunologically effective amount of total tumor cell RNA, wherein the tumor cell is of the type associated with the cancer.